

REMARKS/ARGUMENTS

The Office Action stated: that Claims 1 to 8, 21 to 25 and 31 to 36 are currently pending in the instant application; and that, upon reexamining the pending claims, the Examiner has found prior art that reads on the instant invention and will reopen prosecution. The new prior art certainly does not read on any of the claims because there are not any prior art anticipation rejections. Sections 102 and 103 rejects only with claimed inventions, not disclosed inventions. The obviousness rejection is in error factually and in error in law.

Claim 34 has been amended to put it in independent form.

The Office Action stated that applicant's amendment, filed on December 26, 2007, has overcome the objection of Claims 1 to 8, 21 to 25 and 31 to 34 as containing non-elected subject matter and this objection has been withdrawn.

The Office Action stated that following is a quotation of 35 U.S.C. § 103(a) that forms the basis for the obviousness rejection set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The Office Action stated: that *Graham v. John Deere Co.* set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a); see *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); and that, specifically, the analysis must employ the following factual inquiries:

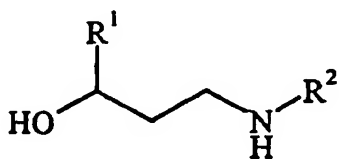
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The Examiner has correctly stated that the above factual inquiries are required. In fact, the first three factual inquiries are mandatory and have to be determined in the record (along with identification of the support facts, and the analysis). The Patent Office policy is to follow the Graham decision. The recent Supreme Court's KSR decision affirmed its Graham decision and asserted that the first three factual inquiries are necessary in all decisions under 35 U.S.C. 103(a). The Examiner has not resolved in the record the factual inquiry of what is the level of ordinary skill in the pertinent art, hence the rejection is defective, and the obviousness fails. The Examiner has the burden of proof and he has not carried his burden. The Examiner also has not factually and/or legally shown in the record that the claimed invention is prima facie obvious.

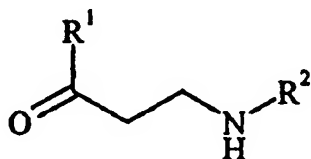
Claims 1 to 8, 21 to 25, 31 to 33, 35 and 36 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill et al. Applicant traverses this rejection.

Applicant, in the instant invention' claims a process for the preparation of a compound of formula:



and/or an addition salt of a proton acid, wherein R¹ represents C₁₋₈-alkyl or phenyl and R² represents alkyl, cycloalkyl, aryl or aralkyl, each aryl or aralkyl being optionally further substituted with alkyl, alkoxy and/or halogen, which process comprises the following steps: a) reacting a mixture comprising: (i) a methyl ketone of formula: CH₃COR¹ wherein R¹ is as defined above, and (ii) a compound of formula: H₂N-R² and/or an addition salt of proton acid, wherein R² is as defined above, and (iii) formaldehyde or a source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-

trioxane, paraformaldehyde and mixtures thereof, in the presence of a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof and optionally a proton acid to provide a β -keto amine of the formula:



and/or an addition salt of a proton acid and b) reducing the carbonyl group of (β -keto amine to afford a compound of formula 1 and/or an addition salt of a proton acid wherein the step a) is carried out at a pressure above 1.5 bar.

The Examiner tried to make a showing of prima facie obviousness, but failed. Even if the Examiner had made a showing of prima facie obviousness, applicant has rebutted and destroyed it.

The differences between applicant's Claim 1 and the disclosure of Hill et al. inventive, patentable and unexpected over Hill et al. Applicant's Claim 1 primarily differs from Hill et al. by working under a pressure of at least 1.5 bar. This difference in pressure surprisingly is sufficient to achieve a complete change in product composition from Hill et al.

Hill et al prepared tritium labeled compounds according to known methods. According to the literature Hill et al. expected (page 813, fourth and fifth paragraphs) and obtained only low yields. In some experiments with derivatized starting compounds it was not possible even to separate the desired secondary Mannich base (secondary amine) from the reaction mixture. If the present process would have been obvious to the person skilled in the art, Hill et al. clearly would have applied modest pressure to obtain remarkably higher yields. This applies especially in a case where highly dangerous and expensive radioactive labeled compounds have to be handled.

It should be noted that starting from compounds where R^2 is an optionally substituted alkyl residue, the reaction without pressure gives only a small amount of the desired product. Sometimes no secondary base can be isolated at all. For such starting compounds the tertiary amine of formula III is the

main product of the reaction below atmospheric pressure.

In the literature (Mannich et al., 1922, Blicke et al., 1942, and Becker, 1969, all documents cited in the application) it has been demonstrated that unless R^2 is a bulky residue formation of the tertiary base (tertiary amine) prevails by far over the formation of the secondary Mannich base (secondary amine). Decomposition of the tertiary amine of formula III can occur to form the secondary amine in poor yield by applying, for example, steam distillation while the major part of the product forms a brown to black sticky pitch-like mixture.

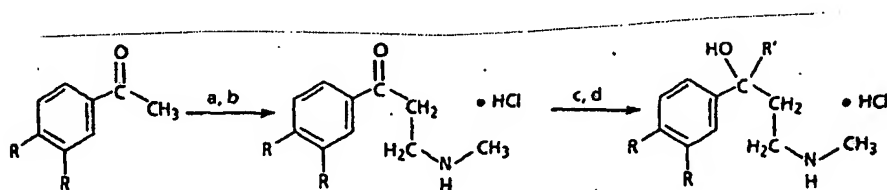
Applying pressure according to applicant's patentable process almost completely avoids formation of the tertiary amine and yields the secondary amine almost free of decomposition by-products regardless which residue R^2 is attached to the amine source. Hill et al. is not even suggestive of this unexpected result.

Thus, applying pressure above atmospheric pressure does not only improve the yield but also makes it possible to directly obtain any desired tertiary amine. This patentable over Hill et al.

Hill et al. does not provide any (strong, weak or otherwise) showing of prima facie obviousness. To the contrary, Hill et al. makes the claimed invention unobvious to one ordinarily skilled in the art.

In trying (unsuccessfully) to establish a case of prima facie obviousness, the Office Action had the heading "The Scope and Content of the Prior Art (MPEP §2141.01)".

The Office Action stated that Hill et al. teaches the following method:



wherein a) $(\text{HCHO})_n$, MeNH_2 HCl , EtOH , HCl , reflux; b) H_2O , steam distillation, MeOH ; c) NaBH_4 , 2-propanol/ H_2O ; d) MeOH , HCl ; $\text{EtOH}/\text{Me}_2\text{CO}$; R is H or Cl . Hill et al. does not teach or suggest the use of the higher pressure.

The Office Action had the heading "The Difference Between the Prior Art and

the Claims (MPEP §2141.02)". The different results obtained by the difference in reaction pressure is unexpected and shows the unobviousness of the claimed".

The Office Action stated that the difference between the prior art of Hill et al. and the instant invention is that there is that step a) in the instant application is carried out at a pressure above 1.5 whereas in the prior art reference the first step is carried out under reflux and then steam distillation. Applicant has shown that the use of the higher reaction pressure results in a surprisingly complete change in product composition plus other unexpected results. This is not a mere modification of process conditions because of the unexpected results obtained by applicant that are not taught or suggested by Hill et al. to one ordinarily skilled in the art. Please remember that the Examiner has not resolved (as is mandatory) the ordinary level of skill in the art, hence the Examiner not know what would be obvious to or anything else about one ordinarily skilled in the art.

The Office Action had the heading "Prima Facie Obviousness – The Rational and Motivation (MPEP §2142-2143)". The unexpected results shown that no prima facie showing of obviousness has ever existed or been established.

The Office Action stated that In re Aller, 220 F.2d 454, 105 USPQ 233 (CCPA 1955), it was well established that merely modifying the process conditions such as temperature and concentration is not a patentable modification absent a showing of criticality. Applicant traverses this statement. The cited CCPA decision is not controlling since it does not comply with the Supreme Court's Graham decision (nor with Patent Office policy). The Examiner should note that the cited CCPA case has a date of 1955 which is a decade before the controlling Graham decision. Furthermore, applicant have shown a criticality in the use of the claimed pressure.

The Office Action stated that, for example, it is obvious to modify the preparation of a compound of comprising step a) and step b) as disclosed in Claim 1 to improve the product yield since a similar reaction using different conditions in step I was already taught by the prior art.

Applicant traverses this statement and has shown above that it is not obvious to one ordinarily skilled in the art to use the increased reaction pressure. The Examiner's statement of "obvious to modify" is meaningless under Section 103(a) because he has not even stated to whom (let alone the person require by the statute) would be obvious to do such modification.

The Office Action stated that, specifically, changing the reaction conditions of step 1 as seen in the Claim 1 absent unexpected results is deemed obvious over the Hill et al. reference.

The Office Action stated that, therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to attempt to improve the known process by modifying the reaction conditions (i.e., carrying out the first step under pressure) to increase the product yield.

The Office Action stated that a strong prima facie obviousness has been established. This statement is totally wrong and has no support if the record of this case. No showing, of any type, of prima facie obviousness has been established. In fact, the opposite is so because the Examiner did not even discuss the achieved complete change in product composition. No prima facie obviousness could be established in the record because the Examiner has not made the mandatory determination of one ordinarily skilled in the art, and the Examiner has not overcome (or even addressed) the unexpected results achieved by applicant's increased temperature.

MPEP §2141.I states:

"Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquiries enunciated therein as a background for determining obviousness are as follows:

(C) Resolving the level of ordinary skill in the pertinent art; and

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The Patent policy shows that no prima facie obviousness has been establish and that the obviousness rejection itself is defective.

This rejection should be withdrawn and the claims allowed.

The Office Action stated: that dependent Claim 34 is also objected to as being dependent upon a rejected based claim; and that, to overcome this objection, applicant should rewrite said claims in an independent form and include the limitations of the base claim and any intervening claims. Claim 34 has been rewritten in such independent form. Applicant thanks the Examiner for indicating the allowability of Claim 34.

Reconsideration, reexamination and allowance of the claims are requested.

Respectfully submitted,

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Date

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